Evidence Report/Technology Assessment Disposition of Comments Report

Research Review Title: Treatment of Depression During Pregnancy and the Postpartum Period

Draft review available for public comment from Sept.11, 2013 to Oct. 8, 2013

Research Review Citation: McDonagh M, Matthews A, Phillipi C, Romm J, Peterson K, Thakurta S, Guise J-M. Antidepressant Treatment of Depression During Pregnancy and the Postpartum Period. Evidence Report/Technology Assessment No. 216. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2007-10057-I.) AHRQ Publication No. 14-E003-EF. Rockville, MD: Agency for Healthcare Research and Quality; July 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
TEP Member #1	General	General Comments: My impression is that this is not one of AHRQ's stronger reports but a large part of this lies with the lack of data that the authors outline quite nicely. There are few studies that compare outcomes in depressed untreated and depressed treated women. However, one wonders about the selection of those groups as the gold standard. While we think of a comparison of these two groups as adequately controlling for the effects of depression, that is not entirely clear. Some pregnant women with depression have an illness so severe that they cannot be free from antidepressant treatment and some women meet criteria for major depressive disorder but the condition is short-lived and it is milder and they may elect to forgo antidepressant treatment. Comparing those two groups may not be substantially different than comparing women with a history of depression to women who are being treated for depression. On top of this, the data showing that depressive disorders have a deleterious effect on birth outcomes is not strong (certainly not as strong in unselected populations as the consistent data that evaluated the effects of SSRIs). In fact, the potential untoward effects of depression on birth outcomes is mentioned throughout the report and it is very problematic. The meta-analysis by Grote et al found very small effects of depression on birth outcomes that may be attributable to confounding. On top of women being in distress because they are depressed, the additional message we are sending them is that they are potentially increasing birth complications because they have an illness they don't want—and the data are not that strong!	Confounding by indication is certainly a concern for observational studies – where it is possible that women with more severe symptoms receive antidepressants while those with less severe symptoms do not. High quality observational studies take measures to control for such confounding and can use more advanced methods such as propensity score matching. Randomized controlled trials of course would help to remove this bias. Even if the effects of depression on birth outcomes are small, we do not feel that an alternative is to compare to women who are not depressed at all. The comparison to no treatment is only one of our comparisons – we were equally interested in competing intervention comparisons. We emphasize the problems with comparisons to a group of women who are mainly not depressed because there is a large body of evidence making such comparisons and conclusions based on this evidence base are likely flawed. The conclusions of the Grote review are "Women with depression during pregnancy are at increased risk for PTB and LBW, although the magnitude of the effect varies as a function of depression measurement, country location, and US socioeconomic status. An important implication of these findings is that antenatal depression should be identified through universal screening and treated" While the risk in the US was lower than in developing countries, it was significant. Socioeconomic status may be an important modifying factor, but does not argue against the risks associated with depression during pregnancy and birth outcomes.
TEP Member #2	General	General Comments: This is a very important report. However, by combining the potential impact in both the prenatal and postpartum periods into each aim I think the report is less useful and the issues are confused. The exposures, the outcomes and the biological and environmental mechanisms related to the outcomes are very different when baby is exposed in utero and postpartum when baby is potentially exposed via breast milk but also exposed to impact even if bottle fed. I strongly encourage you to separate the aims and the diagrams.	This is an excellent suggestion; we have separated these populations into two separate analytic frameworks and have separated the results and discussion of the two populations more clearly.

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TEP Member #9	Executive Summary	ES3, line 44. Decrease in suicide as a benefit. As written, sounds like maternal suicide is a benefit. Please clarify.	The text was changed to: "For example, because a decrease in suicidality is a goal of treatment, we classified reduction in maternal suicide as a benefit?" Also added 'reduced' maternal suicide to analytic framework.
TEP Member #10		Methods: Analytic Framework (explanation) ES3 [p. 11] I read the explanation of how harms and benefits can be categorized (several times) and while I understand it, I wonder if it couldn't be written more clearly OR, additional information reviewed from the "input from experts" to help/convince readers of this categorization. I don't think it is very intuitive and a better explanation might help users of the report (e.g. policymakers)	We divided the analytic frameworks into two, one for pregnant women and one for postpartum women. The analytic frameworks below illustrate the population, interventions, outcomes, and adverse effects studied and their relationship to the key questions. The first framework relates to pregnant women with depression (far left) who receive treatment. This population was intended to be women with a episode of depression beginning during pregnancy, rather than a continuing episode. The exception was Key Question 2e, where the population was intended to be taking an antidepressant during the time of conception. Treatment leads to health outcomes in the box on the far right of the figure, connected by the overarching line. This evidence is the topic of key question 1, as marked on the line. Treatment may lead to intermediate outcomes, such as changes in level of depression symptoms, or adverse events – both noted as separate boxes on the diagram. The evidence showing that improvement in intermediate outcomes (e.g. symptoms) results in improvement in health outcomes (e.g. reduced risk of suicide) is represented by a dotted line between boxes and was not reviewed in this report. The second framework represents postpartum women with depression (far left), and again the outcomes that may result from treatment are depicted in relationship to each other, the treatments, and key questions. The outcomes considered differed from those considered for pregnant women.
TEP Member #10	ES2 (p10)	Key Q 2: Formatting not consistent with KQ 1, even though categories are the same/identical (in some cases)	This is due to the additional question on the risk of teratogenicity with exposure to antidepressants during the time of conception. We have corrected this, and instead made the question on teratogenicity to be item 'e'.
TEP Member #10	ES 5 (p. 13)	Interventions Reword 2nd sentence to avoid using double "nots"	Changed to: "Drugs no longer commonly used were not included"
TEP Member #10	ES13 (p. 21)	Child Harms This section (first paragraph) was a bit vague and didn't "stand alone" like the maternal harms paragraph that preceded it. It was as if you needed the paragraph before to put it in context. I would worry that if someone were quoting the child harms summary by itself, it wouldn't be as clear as it should be.	Text at the beginning of the paragraph changed to: "Evidence on harms to the child of a mother treated for depression during pregnancy, was limited by the comparison groups selected by most studies (pregnant women who did not take an antidepressant, and with unknown depression status in compared groups). As with comparative benefits to the child, the direct evidence is very limited and is mostly insufficient for drawing conclusions."

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TEP Member #10	ES14 (p. 22)	2nd paragraph First sentence: split infinitive?? Reads awkwardly	Shortened the sentence to: "We found no direct evidence on the risk of neonatal withdrawal symptoms or pulmonary hypertension with maternal use of antidepressant drugs to treat depression during pregnancy."
Peer Reviewer #3	Executive Summary	General Comments: Target population, audience and key questions are clear and appropriate. Overall, I was left with the message "there is no evidence" with nothing to guide treatment for women. In the implications, the authors note that there is no evidence regarding breastfeeding, but continue to state that providers should not necessarily discourage breastfeeding and the authors seem very pro-breastfeeding (pg ES-17, line 40) While I agree with the authors about breastfeeding, I would suggest that they could also be "pro-treatment" in a parallel manner (even though there is no evidence for treatment of depression during pregnancy, the authors could be more "pro-treatment").	The sentence: "Based on the best evidence available today, the comparative benefits of treatment to mothers are unclear." was removed. Changed language to: "Although we believe that treatment with antidepressants is likely to improve some symptoms based on evidence in nonpregnant patients, it is possible that individual drugs may have varying effects in pregnant women due to changes in pharmacokinetic parameters. Current evidence is insufficient to address comparative efficacy in pregnant women. Similarly, the evidence on functional outcomes for the mother is unfortunately insufficient, although it leans towards better outcomes in women treated with an SSRI compared with untreated pregnant women Evidence for other health outcomes in pregnant women is missing."
TEP Member #10	ES17 (p.25)	2nd paragraph In regards to relevance to the CHIP program, is it importance or a matter of relevance that a large number of studies are non-US?	Sentence modified to remove 'importance': "The large number of studies conducted in non-US healthcare settings and in samples of women with medium socioeconomic status may limit the applicability of the evidence to the population of children served by the CHIP program as well."
TEP Member #10	ES18 (p. 26)	1st paragraph The last sentence (when making direct comparisons….) reads awkwardly; next paragraph, insert neonatal to describe respiratory distress since the preceding sentence was referring to pregnancy. Otherwise, it might be construed as maternal respiratory distress. The last sentence in paragraph 2 is awkward, too.	1 paragraph sentence changed to: "While the direct evidence does not indicate higher rates of preterm birth with use of SSRIs during pregnancy, unadjusted odds ratio of 1.73 (95% CI 0.63 to 4.42), it is insufficient to guide clinical decisions." Changed to "neonatal respiratory distress"
TEP Member #10	ES19 (p. 27)	Limitations (last paragraph Perhaps substitute "inform" for "support"	Changed to: "The current evidence base is insufficient to inform clinical decisionmaking fully, because it requires knowing both benefits and harms and being able to determine the tradeoffs of individual choices"

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Public Commenter	Executive Summary	This AHRQ draft report provides a valuable contribution in highlighting major gaps in the research on the pharmacological treatment of depression during pregnancy and the postpartum period. It underscores the fundamental need for better characterization of the population being treated and studied, e.g. whether women are being treated with an antidepressant due to depression, as well as the research necessity of reporting diagnostic and treatment data. We feel that the Abstract and Executive Summary (ES) as written, however, may be misinterpreted as concluding that antidepressant medications have been shown to have no effectiveness in pregnant and postpartum women and that, furthermore, they may be linked to autism spectrum disorder, congenital anomalies and ADD in the offspring.	ES-17: The sentence: "Based on the best evidence available today, the comparative benefits of treatment to mothers are unclear." was removed. Changed language to: "Although we believe that treatment with antidepressants is likely to improve some symptoms based on evidence in nonpregnant patients, it is possible that individual drugs may have varying effects in pregnant women due to changes in pharmacokinetic parameters. Current evidence is insufficient to address comparative efficacy in pregnant women. Similarly, the evidence on functional outcomes for the mother is unfortunately insufficient, although it leans towards better outcomes in women treated with an SSRI compared with untreated pregnant women Evidence for other health outcomes in pregnant women is missing." The potential link to autism disorder and ADHD with either depression or use of antidepressants during pregnancy is unclear, but still a concern. The discussion on this evidence begins with: "Whether autism spectrum disorder (ASD) is associated with depression during pregnancy, antidepressant treatment, or an interaction of the two is not clear."

Commentator & Affiliation	Section	Comment	Response
Public commentator	Specific comments	Even though on p. ES-1 the authors establish the framework that antidepressants have been proven effective in non-pregnant adults and that there is the presumption that medications in general "...remain effective in pregnancy," earlier on p. vi of the Abstract, there is the standalone statement in the Results section that says, "Evidence is insufficient for treatment in the postpartum period..." as well as later on p. ES-11, "The overarching finding... is that little evidence exists on the maternal benefits of antidepressant therapy during pregnancy..." A reader might interpret this to mean that antidepressants are not effective during pregnancy. We appreciate the challenge to explain the complexities of the state of the science, and that one cannot draw conclusions on benefits and harms since, as is said on p. ES-11, "Studies were generally not designed to measure benefits..." The reviewed studies likely did not seek to prove the effectiveness of antidepressants with pregnant and postpartum women since this class of medications has previously been shown to be effective overall in numerous populations, as referenced by Gartlehner's 2011 AHR antidepressant meta-analysis. We strongly recommend that the conclusion from this systematic review (i.e. "that little evidence exists on the maternal benefits of antidepressant therapy during pregnancy") be placed in context each time it is written in both the Abstract and ES, meaning that conclusions cannot be drawn about the benefits of antidepressants in pregnant and postpartum women from this reviewed set of studies due to the study limitations and the fact that these studies were not generally designed to measure benefits. Therefore, based on the existing body of research, which demonstrates the effectiveness of antidepressants in numerous populations, there is no evidence indicating that antidepressants would be any less effective in pregnant and postpartum women than they are in other women.	The sentence: "Based on the best evidence available today, the comparative benefits of treatment to mothers are unclear." was removed. Changed language to: "Although we believe that treatment with antidepressants is likely to improve some symptoms based on evidence in nonpregnant patients, it is possible that individual drugs may have varying effects in pregnant women due to changes in pharmacokinetic parameters. Current evidence is insufficient to address comparative efficacy in pregnant women. Similarly, the evidence on functional outcomes for the mother is unfortunately insufficient, although it leans towards better outcomes in women treated with an SSRI compared with untreated pregnant women Evidence for other health outcomes in pregnant women is missing."

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Public commentator (continued)	Specific comments:	The Abstract & ES conclusions, as written, may have the untoward effect of encouraging researchers to submit research proposals without fully considering the challenges of research in pregnant women as well as the question of whether funding agencies are likely to support further interventions studies in an area (antidepressant treatment of depression) in which efficacy and effectiveness have been well-established. These concerns may be addressed by stating the conclusions within the context of the wider body of antidepressant research, as suggested above.	The Gartlehner review certainly establishes the comparative effectiveness of antidepressants compared to each other, although work by Turner reveals serious reporting bias in antidepressant studies compared to placebo drawing the assumption of efficacy vs no treatment into question. Regardless the existing bodies of evidence in nonpregnant populations do not address the long list of outcomes specific to pregnant and postpartum women identified as important by our technical experts (e.g. mother-infant bonding). The current studies make no attempt to assess these outcomes and the wider body of antidepressant research is not useful. Future research studies should be designed in the populations of interest, make comparisons that are relevant, and measure these important outcomes that are specific to pregnancy and postpartum.
		We agree that it is very important to understand the risks of antidepressant treatment to pregnant and postpartum women and offspring, as well as the risks of depression to pregnant and postpartum women and offspring. However, regarding the standalone recommendation on p. vi of the Abstract that "...future research should focus on the risk of congenital anomalies and the diagnosis of autism spectrum disorder or attention deficit disorder in the child associated with antidepressant use for depression in pregnancy," it is unclear whether the signal evidence from this systematic review warrants singling out these three risks, as it does not appear that there were sufficient research studies to allow for a meta-analysis. It may be helpful to include from a public health viewpoint a contextual statement in the Abstract (as it is in the ES on p. 18 in relation to autism spectrum disorder),that if these risks hold up with further research, they would account for only an extremely small percentage of the cases of these three risks.	Abstract text modified to: "Signals from this indirect evidence suggest future research should focus on the comparative risk of congenital anomalies and although a small potential increase in overall risk, the diagnosis of autism spectrum disorder or attention deficit hyperactivity disorder in the child associated with antidepressant use for depression in pregnancy." We feel the signals are more than adequate to warrant future research as there are numerous studies showing potential harm with specific antidepressants; meta-analyses were performed on congenital anomaly and ASD data. Future studies could establish which treatments are/are not associated with increased risk to make treatment decisions more clear.
TEP Member #1	Introduction	Introduction: As noted above, the way in which depressions impact on birth outcomes is rendered is inaccurate.	Text changed to: "Although causation has not been proven, several adverse obstetric complications have been reported with untreated prenatal stress and depression, including pre-eclampsia, preterm delivery, low birth weight, miscarriage, small-for-gestational-age babies, low Apgar scores, and neonatal complications.[4, 5]"

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TEP Member #1	Introduction	p. 9, line 15. We do not know the directionality of some of the harmful prenatal behaviors and depression. It is also possible that some issues such as alcohol or substance misuse lead to depression.	Modified sentence to focus on other harms of maternal depression. Added a notation that alcohol and substance abuse are associated with depression." Depression during pregnancy is known to lead to harmful prenatal health behaviors such as poor nutrition, poor prenatal medical care and risk of suicide, and is associated with smoking, alcohol or other substance misuse, each of which compromises the health of both the woman and her fetus.[2, 3]"
TEP Member #1	Introduction	p.9, line17-21. It is not accurate to say that these outcomes are associated with "untreated" stress and depression since studies did not always control for depression treatment.	Modified sentence to focus on other harms of maternal depression. Added a notation that alcohol and substance abuse are associated with depression." We removed the mention of untreated stress from this sentence." Although casation has not been proven, several adverse obstetric complications have been reported with untreated prenatal depression, including pre-eclampsia, preterm delivery, low birth weight, miscarriage, small-for-gestational-age babies, low Apgar scores, and neonatal complications.[4, 5]"
TEP Member #1	Introduction	p.17, line 29 should be treated "non-pharmacologically" not non-pharmacologic	Corrected.
TEP Member #2	Introduction	I think it is strange that you use a citation to a book from 2008 for the incidence and prevalence and impact of prenatal and postpartum depression. Maybe you are trying to save space but really goes against what most people think of in high quality reason settings and publications. No discussion of potential impact of exposure in both periods. combined.	We have added another citation from 2011 (Kayser et al), and two other citations. These are the most up-to-date prevalence data available.
Peer Reviewer #3	Introduction	The introduction was clear and appropriate.	The report authors acknowledge and appreciate the comment.
Peer Reviewer #4	Introduction	Good job defining background (condition), scope of effect of depression on women and their families; however, realize that many women are depressed long before they become pregnant and that this also has an impact both during and after their pregnancy.	The report authors acknowledge and appreciate the comment.

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Peer Reviewer #4	Introduction	For treatment strategies, very heavy on background with respect to pharmacologic therapies. If the scope of the review is to provide an analysis of pharmacologic therapies in comparison to non-pharmacologic therapies, reference 11 (Freeman, et al) alone is not strong enough (highlighting primarily complementary medical therapies) as a representative comparison. As noted above, there are many variant forms of psychotherapy, however as viewed in the review, all are placed under 'various psychotherapies.' I understand that this was done to better inform the comparison versus pharmacologic therapies, however it is difficult to say all counseling modalities fall under the same treatment umbrella (similar outcomes, etc.). There are likely notable differences in outcomes and the provision of care between cognitive behavioral therapy, interpersonal therapy, motivational interviewing, forms of group therapy, etc. This is of particular importance if looking into the effectiveness of clinical therapies across variant socioeconomic groups, which is an underlying issue with this report as well. Also no discussion on various uses of technology in treatment for depression (e.g. internet-based therapies, web-camera counseling, mobile phone applications); this is a quickly growing area of research, particularly based on the mobility of the US population and the ubiquity of the Internet and mobile phone access.	Because the purpose of the report is to compare pharmacologic treatments to each other and to other treatments such as those discussed here, the focus in the introduction is primarily on pharmacological treatment and the discussion here of nonpharmacological is simpler because it is an example only. We have added citations, one on electroconvulsive therapy and three on different forms of psychotherapy: Kayser, 2011; Cuijpers, 2011;Ishak, 2011;Nieuwsma, 2012. While our list of comparison interventions does not separate out all forms of psychotherapy, we considered them separately in the results. We have added citations to the discussion about the use of technology in treating depression. "Newer approaches to non-pharmacological interventions using technology such as internet-based therapies, web-camera counseling, and mobile phone applications are emerging and may offer pregnant and postpartum women alternatives to more established treatments, particularly in lower-income or rural populations. [Aguilera, 2011 #10868;Boschen, 2008 #10866;Moritz, 2012 #10867]" ES-20 and on page 69 of the report.
Peer Reviewer #4	Introduction	Key questions and analytic framework reasonable for evaluation.	The report authors acknowledge and appreciate the comment.
TEP Member #5	Introduction	Given that maternal depression (parental mental health problems) is one of the Adverse Childhood Experiences identified by Fellitti, the impact for children goes beyond developmental health and can potentially impact lifelong health trajectories (obesity, heart disease, COPD, autoimmune diseases, etc. have all been linked to ACEs). It might be worth mentioning this in the introduction.	While we do agree that these are potential long-term consequences, we have included these as outcomes in the report but that adding them to the introduction may be beyond the scope since the focus is only on the pregnancy and postpartum periods and does not extend into maternal depression during later childhood.
TEP Member #6	Introduction	There seems to be two introductions, I thought I had finished it and then there was another introduction	There is an executive summary and then the full report, starting with a full introduction.
TEP Member #7	Introduction	ok	No comment.
TEP Member #8	Introduction	The introduction clearly describes the context.	The report authors acknowledge and appreciate the comment.

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TEP Member #10	Introduction	Overall, the introduction is well-done.	The report authors acknowledge and appreciate the comment.
TEP Member #11	Introduction	Seems a thorough lit search	The report authors acknowledge and appreciate the comment.
TEP Member #1	Methods	I found the way in which data were organized into direct and indirect evidence confusing.	The authors appreciate that not all readers will be familiar with these terms. We have reviewed the text to determine areas where we can improve the discussion of the terms. We have added the following to the methods sections: "Direct comparisons were preferred over indirect comparisons. There are three types of directness considered; populations, intervention comparisons, and outcomes. Studies that include the population of interest (depressed pregnant or postpartum women) in both intervention and control groups make the comparisons of interest (pharmacological treatments compared with each other, nonpharmacological interventions or no treatment) and measure outcomes of interest directly (not using proxy measures, e.g. laboratory values) are direct evidence."
TEP Member #2	Methods	Methods are very well done. they are clearly presented. The assessments for prenatal and postpartum are done separately as they must be. Make the aims fit what you did.	The report authors acknowledge and appreciate the comment.
Peer Reviewer #3	Methods	Methods were appropriate.	The report authors acknowledge and appreciate the comment.
Peer Reviewer #4	Methods	Inclusion and exclusion criteria clearly stated and justifiable. Search strategies clearly delineated and logical. Only issue as discussed above in that comparators to pharmacologic therapy include 'any' non-pharmacologic therapy, of which there remains a wide variety and heterogeneous effectiveness profile based on specific populations.	The report authors acknowledge and appreciate the comment. As noted above, we understand the diversity of nonpharmacological treatments and would have included any that were studied. As noted in the report we found very few studies making the comparisons we were interested in, such that further delineation of the various types of interventions was not necessary.
Peer Reviewer #4	Methods	Yes	The report authors acknowledge and appreciate the comment.
TEP Member #6	Methods	Yes	The report authors acknowledge and appreciate the comment..
TEP Member #7	Methods	the methodology is very sound	The report authors acknowledge and appreciate the comment.
TEP Member #8	Methods	The methods are state-of-the-art and appropriate for the key questions.	The report authors acknowledge and appreciate the comment.
TEP Member #9	Methods	well laid out. especially issues related to comparability of specific groups and accounting for risks of underlying depression.	The report authors acknowledge and appreciate the comment.

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TEP Member #11	Methods	Inclusion and exclusion criteria seems justified, as the study aimed to focus on depression and not other symptoms or disorders. Seems effective to include studies with pregnant women receiving antidepressants for unknown or mixed.	The report authors acknowledge and appreciate the comment.
TEP Member #1	Results	p.20, line 30. Would the Cohen JAMA study (2006) and the Yonkers Epidemiology (2011) study be informative re the benefit of pharmacological treatment in pregnancy?	Both studies address relapse of depression in women with a history of depression that become pregnant. Some are continuing treatment with an antidepressant (in remission) depression and some are not. These studies are appropriate to address a different question than we are addressing here - treatment of a current episode of depression.
TEP Member #1	Results	22, line 44. The risk of teratogenicity was ... was examined in few well designed studies? This is surprising since SSRI exposure, in particular, is one of the best studied medication exposures in pregnancy.	For our review, we were looking specifically for exposure during the conception period. Most of the evidence on SSRIs relates to *any* exposure during early pregnancy and often the studies cannot be precise about when exposure began due to the methods used to identify exposure. The exposure in early pregnancy (1st trimester) is reviewed in the section on pregnancy. Changed to: "The risk for teratogenicity with exposure to antidepressants specifically during the conception period was examined in few well-designed studies that were able to identify exposure during this period such that the evidence was insufficient. Numerous other studies examined congenital malformations with exposure in early pregnancy but did not report on exposure during the conception period (i.e. pre-existing treatment). These studies contributed to the evidence on potential harms with treatment during pregnancy."
TEP Member #1	Results	P.22. There is some work that explored benzodiazepine exposure (with and without SSRI) in pregnancy and neonatal distress. There is a suggestion that benzodiazepine use may complicate interpretation of the SSRI findings.	We agree that benzodiazepine use is a potential confounding factor for adverse neonatal outcomes. We examined this whenever it was reported. More recent studies report much lower prevalence of use (if any), but many studies are silent on this type of co-exposure. We have added text to the discussion on page 64: "For all other subgroups (including coadministration of other drugs, medical provider characteristics, medical care environments, and characteristics of diagnosis) the evidence is limited. For example, co-administration of antidepressants and benzodiazepines in pregnant women may modify or confound adverse outcomes in neonates, but most studies did not report on this exposure. This may be due to decreasing prevalence of benzodiazepine use, but we are not able to draw conclusions."

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TEP Member #2	Results	Well presented but again do not ever lump the two periods. We have enough trouble being able to do studies to assess outcomes. Lumping the periods suggests that there are problems potentially in the postpartum period when the problems were really only identified during pregnancy.	We appreciate this comment. We did not intend to lump the pregnancy and postpartum periods and they are separated into two separate analytic frameworks, and the results for each are more clearly separated...
Peer Reviewer #3	Results	Results were appropriate.	The report authors acknowledge and appreciate the comment.
Peer Reviewer #4	Results	The results section is appropriately detailed, with the characteristics of included studies well described. The figures and tables also are appropriate, provide an adequate picture and are descriptive.	The report authors acknowledge and appreciate the comment.
TEP Member #5	Results	Yes - detail is appropriate. One clinical question I had in reading the section on child development and the effects of SSRIs - where treatment was associated with lower scores in gross motor development. Without a comment about the severity of depression - the SSRI group may have represented more severe depression (requiring treatment) that may have had impacts on development in its own right. Were the treated mothers symptom-free, or did they still have clinical depression? If these questions were not addressed by the researcher, the depression itself may have been a confounding factor in their findings.	In this very small study, depression was measured in two ways; the BDI and a Likert scale. Neither showed statistically significant differences between groups, although the study size makes identifying significant differences difficult. We added the following to the discussion of evidence: "Beck Depression Index maximum scores were 24.0 in the untreated group and 21.3 in the treated group, P=.58. "
TEP Member #6	Results	Way too much information	The report authors acknowledge and the comment.
TEP Member #7	Results	the studies are listed as to types of bias. There are very few critical analyses of specific studies to allow the clinician to decide whether or not the methodology of the study supports the conclusions e.g. in the Croen's study linking SSRIs to ASD, there is no certainty as to whether the women actually took the medication	We have tables in the report where individual study assessments are presented. The concern about exposure ascertainment is noted, and certainly filling a prescription does not guarantee exposure although the consistent refilling of the prescription does support the theory.
TEP Member #8	Results	The results are clearly and comprehensively presented.	The report authors acknowledge and appreciate the comment.
TEP Member #9	Results	yes	The report authors acknowledge and appreciate the comment.
TEP Member #10	Results	Approach to presentation was very clear and systematic	The report authors acknowledge and appreciate the comment.
TEP Member #10	21 (p. 50) Breastfeeding	The first sentence refers to pregnancy, not breastfeeding leaving reviewer to wonder if this was a mistake. Also, for reporting in this section, what is RRR? (not used to seeing this)	Changed to: "No direct evidence was found on the effect of SSRIs used during pregnancy on breastfeeding outcomes postpartum." Added definition for RRR: relative risk reduction (reported in the study rather than relative risk)

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TEP Member #10	37 (p66) Congenital Anomalies	What are the # signs about? Total N??	Corrected.
TEP Member #10	55 (p.84) Postpartum Exposure	For depression severity level, this summary statement was not clear. To understand it, I had to draw the independent and dependent variable. (especially compared to the next statement on duration of treatment— much more clear)	Changed to: In women with postpartum depression, symptom response brief dynamic psychotherapy, with or without sertraline, does not vary based on depression severity level."
TEP Member #10	55 (p.84 Detailed Assessment	First sentence of this section is awkward ; also, in the last sentence, add study to randomized control_____of women.	Removed first sentence. Changed second sentence to: "There were six medium to low risk of bias observational studies of the comparative effectiveness of pharmacological and nonpharmacological treatments in women with depression during pregnancy" Last sentence – correct to 'randomized controlled trial'
TEP Member #11	Results	I have some question about the strength of the rationale to include indirect evidence from the 104 observational studies of pregnant women receiving antidepressants for mixed or unreported reasons and compared with pregnant women not taking antidepressants whose depression status was unknown. There seems to be many variables in these data that would affect the outcomes in analysis	The authors understand these concerns and wish to make it clear that this body of evidence is not sufficient to answer the clinical questions that are largely inadequately answered by the current direct evidence. However, there are others who feel that this evidence is better than no evidence so we include it here and use it only where there is a gap in the direct evidence and where the outcome is a serious harm.
TEP Member #1	Conclusion	Discussion/ Conclusion: This was stronger although again, there is this assumption that depressed women have terrible birth outcomes, which is not accurate	The report authors acknowledge and the comment. Please note that the introduction of the concept that birth outcomes may be worse in women with depression was changed to: "Although causation has not been proven, several obstetric complications have been reported with untreated prenatal depression, including pre-eclampsia, preterm delivery, low birth weight, miscarriage, small-for-gestational-age babies, low Apgar scores, and neonatal complications, and may be more common among women with lower socioeconomic status." in the report introduction..
TEP Member #2	Conclusion	Limitation clearly presented. Most of the limitation are in the dearth of data available to analyze and report.	The report authors acknowledge and appreciate the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Conclusion	Discussion/ Conclusion: In the implications (page ES-18, line 6) , the authors state "Our evidence indicates that SSRIs results in no differences on most measures, but may result in slightly worse motor development than no treatment at all, but again this evidence is insufficient to guide clinical decisions." This was not mentioned in the results; the results had stated "direct evidence on infant and child development is limited... insufficient to draw conclusions. Indirect evidence did not indicate increased risk of motor, language or cognitive development" so I was surprised that the implications mentioned potention worse motor development. The evidence is discussed in the full report later, but would add to the results on ES-12, line 33 if they will be in the implications that follow. I agreed with the discussion on ASD, would suggest that your findings suggest the same for ADHD.	The evidence discussed here is insufficient to support conclusions because it is based on a single very small study (n = 44). It is likely that a larger study would change these findings. The sentence has been changed to: "Our evidence indicates that use of SSRIs results in no differences on most measures" We did not feel that the evidence on ADHD was at the same level methodologically as the evidence on ASD, where both studies attempted to analyze the effect of depression and one had low risk of bias.
Peer Reviewer #4	Conclusion	Discussion/ Conclusion: The major findings are clearly stated. The limitations of the reviews and the studies were well described. As noted previously above, applicability to US populations (not only based on lack of direct evidence), but also however on the lack of heterogeneity of studied populations (i.e. socioeconomic status, race) is a critical factor	The report authors acknowledge and appreciate the comment.
TEP Member #10	Discussion	58 (p. 87) The paragraph on ASD: awkward grammar in the sentence beginning: The role of depression was studied in one study…	Changed to "The role of depression was examined in one study through subgroup analyses. Analysis of women with depression who received an SSRI compared with a population of pregnant women who did not receive an SSRI (depression status unknown) found the risk for ASD was statistically significantly elevated with a greater odds ratio than the overall analysis (OR 3.34, 95% CI 1.50 to 7.47), while the risk in women taking an SSRI for another indication was lower and not statistically significant (OR 1.61; 95% CI 0.85 to 3.06)."
TEP Member #10	Discussion	58 (p. 87) Last paragraph: reads awkwardly: the overarching findings for harms…. Also, insert neonatal in front of respiratory distress.	Changed to: "The overarching findings for Key Question 1 on comparative benefits are that there is little direct evidence on the maternal benefits of antidepressants used to treat depression in pregnancy, including important health outcomes such as functional status."
TEP Member #10	Last paragraph	58 (p. 87) Is the reference to Table 10 here correct? Should it be Table 9?	Table numbering corrected.

Commentator & Affiliation	Section	Comment	Response
TEP Member #10	Last paragraph	59 (p. 88) Again, is this table misnumbered/out of order? It states Table 10, below, but the following table is #9…but it is a great table!	Table numbering corrected.
Peer Reviewer #4	Conclusion	Agree with section on future research, however to further inform future depression treatments, would recommend discussion/consideration of growing practice surrounding adjunct therapies (i.e. internet-based therapies, mobile-phone applications, etc.). Three articles were uploaded (Moritz 2012, Aguilera 2011, Boschen 2008) that, though would not meet specific inclusion criteria for this review, may help point the authors towards new methods in provide mental health care, regardless of socioeconomic status (particularly in light of equivocal evidence for therapy). Would also consider separating out forms of psychotherapy (CBT, IPT, MI, etc.). Though the studies do not evaluate pregnant or postpartum women specifically, they do highlight a direction that future mental health therapies may be going and are most applicable to mobile populations without access to mental health care. Such technology-centered therapies offer a powerful adjunct, given their ease, portability, and low cost.	We have added reference to these newer methodologies. Text in executive summary and report discussion changed to: “Newer approaches to non-pharmacological interventions using technology such as internet-based therapies, web-camera counseling, and mobile phone applications are emerging and may offer pregnant and postpartum women alternatives to more established treatments. [Aguilera, 2011;Boschen, 2008;Moritz, 2012]”
TEP Member #5	Conclusion	Discussion/ Conclusion: Yes - though I didn’t get a sense of the future research section in terms of key research questions.	Future research section separated from the limitations of the evidence section to make these points more distinct and clear.
TEP Member #6	Conclusion	No they are not No more research will ever make any definitive conclusions.	We feel that both RCTs and observational studies could be conducted in ways that directly answer the remaining questions, for example comparing treatments to each other in women with depression and measuring the impact of various potentially prognostic factors. Please see the future research questions.

Commentator & Affiliation	Section	Comment	Response
TEP Member #8	Conclusion	Discussion/ Conclusion: The discussion and conclusions are well done, and the future research section clear. The only minor comment I would make is regarding the discussion of research designs on p. 93. There is a fairly strong literature on the ethics of including pregnant women in clinical trials (see, for example, http://www.secondwaveinitiative.org/), and comparative trials of different treatments in depressed women, even if randomized, would likely be considered reasonable given the substantial uncertainty about benefits and harms to both mother and child so elegantly presented in this report. A few more sentences here would be appropriate.	Changed to: "While there is still hesitancy to conduct randomized controlled trials in pregnant women, Howland, 2010 #7876] the assumption that the clinical efficacy of interventions in nonpregnant populations is directly applicable to pregnant women may not be valid for many reasons. Making these types of comparisons requires well-designed prospective studies, with measurement of depression severity at baseline and during followup. Comparisons of specific treatments in pregnancy are badly needed. Such studies are advocated for by various groups (http://www.secondwaveinitiative.org/Home.html, http://blogs.plos.org/bodypolitic/2011/01/06/why-pregnant-women-deserve-drug-trials/) and rules on protecting pregnant women research subjects, their fetuses, and the fathers are outlined by the Department for Health and Human Services."
TEP Member #8	Conclusion	Clarity and Usability: The report is extremely clear, and should definitely be used to inform policy decisions, hopefully mostly in terms of future research.	The report authors acknowledge and appreciate the comment.
TEP Member #8	Conclusion	Discussion/ Conclusion: yes	The report authors acknowledge and appreciate the comment.
TEP Member #10	Conclusion	Discussion/ Conclusion: I expected to see more about the maternal infant dyad, and in particular the differences in the bonding process. Were there no studies that examined this?	No, unfortunately there were not.
TEP Member #11	Conclusion	Discussion/Conclusion: The conclusion clearly states that there is inadequate evidence of benefits and harms to allow well-informed decisions about tx. They acknowledge that the comparison groups were not exclusively depressed women, so the control was not specific enough.	The report authors acknowledge and appreciate the comment.
TEP Member #1	Figures	Tables: shouldn't all studies have documentation of the cohort size in the extraction tables? It happens in most instances but not all.	Corrected.
TEP Member #1	General	Referencing for papers cited was sometimes provided in the text but most often not. It is difficult to read this without references for the original papers that were cited. There is a need for copyediting for grammatical errors.	We appreciate these comments and have added citations were missing and had the report carefully edited.
TEP Member #1	General	Clarity and Usability: no, it was very difficult to follow, especially without references to the reports that were cited.	We appreciate these comments and have added citations were missing and had the report carefully edited.
TEP Member #2	General	Clarity and Usability: I like the structure except as mentioned above for the aims and diagrams that combine the prenatal and postpartum periods.	The report authors acknowledge and appreciate the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	Clarity and Usability: This report was well structures and organized. Because of the lack of evidence, the conclusions cannot inform policy or practice decisions. I believe that some other AHRQ systematic reviews have stated within their abstract that direct evidence was lacking, but based on indirect evidence.... The authors have chosen not to include indirect evidence, but then we are left with little guidance.	The report authors acknowledge and appreciate the comment. We have clarified in the methods section of the report and executive summary that there are three types of indirectness, and we believe That the use of indirect evidence in this case is concerning because it is based on indirect populations, leaving more uncertainty in how to generalize the results than may be true for other types of indirect evidence. Our abstract reports on key outcomes from indirect evidence that should be the subject of future research.
Peer Reviewer #3	General	Abstract on vi states "Signals from this evidence suggest that future research should focus on the risk of congenital anomalies and the diagnosis of autism spectrum disorder or attention deficit disorder..." I would add consider adding preterm birth.	With the addition of another study reporting preterm birth, the evidence is now low strength, and is based on direct evidence. The signals noted here are serious harms found in the indirect evidence.
Public Commenter #1	General	Since the focus of the report is on antidepressant treatment, it may be useful to specify that in the title.	We changed the title to "Antidepressant Treatments in Pregnant and Postpartum Women with Depression"

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General	General Comments: The report is clinically meaningful in that it is an extensive evaluation of the evidence surrounding the medical treatment of depression both during pregnancy and in the postpartum period. Additionally it provides a review of the evidence regarding side effects associated with medical treatment, with particular attention to those that occur within infants. This is of relevance to primary care providers that care for neonatal and pediatric patients in order for them to provide the most accurate counseling to their families based on the risk associated with various medications a mother may be taking during her pregnancy and beyond while breastfeeding. The target population and audience are well defined. The key questions are explicitly stated. Though the review is evaluating treatment, most specifically medical management, the review would be more informed to not categorize all counseling therapies together (i.e. cognitive behavioral therapy, interpersonal therapy, group therapy, motivational interviewing, etc.) and evaluate specific counseling therapies against one another. The equivocal evidence surrounding medication management would push providers (and patients) to more closely consider non-pharmacologic therapies, and defining these separately may hold value in moving forward with non-pharmacologic therapies for depression during pregnancy and the immediate postpartum period.	We have added "We recognize the important differences between these treatments and consider them separately when compared to pharmacological treatments, rather than as a group. "to the description of methods. In the results, we do not combine nonpharmacological therapies, but handle them individually.
Peer Reviewer #4	General	Clarity and Usability: The report is generally well-organized. The main points are clearly presented. From a pediatric primary care perspective, the findings confirm that with no clear benefit for (or against) medical treatment with antidepressants, providers need to have open discussions with families about the need or perceived need to be on medication.	The report authors acknowledge and appreciate the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General	Agree with and appreciated cardiac malformations being evaluated as a separate group. Findings regarding a possible increased risk of autism spectrum disorder with SSRI use (indirect evidence) are particularly notable, as are findings suggesting of an increased risk of ADHD based on SSRI use after pregnancy (up to four years post delivery) and with bupropion use at any point in pregnancy. Clearly defining this risk for families is imperative, but based on the findings, will maintain some ambiguity. Also interesting from a clinician viewpoint (regarding surveillance, evaluation) that those mothers with a history of depressive disorders had children with a significantly higher risk of ADHD at age 5.	The report authors acknowledge and appreciate the comment.
Peer Reviewer #4	General	Also of note is the increased risk of persistent pulmonary hypertension associated with maternal SSRI use late in pregnancy.	The report authors acknowledge and appreciate the comment.
Peer Reviewer #4	General	Another important finding was that, when combined with fluoxetine, multiple sessions of CBT were not superior to a single session. This is particularly interesting as it speaks to the benefit of combination therapy and questions a common belief that clinical benefit will be achieved only following several CBT visits, which according to the evidence, may not actually be required.	The report authors acknowledge and appreciate the comment.
Peer Reviewer #4	General	Regarding the ability to inform practice, particularly in the US. It is notable that 67% of the studies were completed outside of the US. Additionally, the lack of direct evidence makes finding true conclusions (other than the lack thereof) very difficult.	The report authors acknowledge and appreciate the comment.
Peer Reviewer #4	General	Also of note, considerations about socioeconomic status (SES) and access to mental health care should be a part of any discussion with regards to clinical effectiveness of therapy. Within the US, mothers in poverty without access to care have a much more difficult battle versus those with resources (namely insurance, family support, etc.). For those primary care providers practicing in urban settings wit patients who usually align with a low SES, it is unclear if the evidence of the report (based on patients who were primarily white women of medium SES), can truly be applied to the population which they serve.	Text in the Applicability section changed to: “Few studies reported race or socioeconomic status. In the studies that reported race, the populations were predominantly White. When reported, a medium socioeconomic status level was most common, and applicability to lower US socioeconomic groups, including lesser availability of resources (namely insurance, family support, etc.) and access to mental health care is certainly not clear.”

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	General	General Comments: I think the target population and audience are explicitly defined, key questions are appropriate and explicitly stated. In terms of being clinically meaningful - hard to say when the general conclusion is “no evidence” throughout the report. As a clinician, I won’t have much change in my practice as a result of the report.	The report authors acknowledge and appreciate the comment.
Peer Reviewer #5	General	Clarity and Usability: Yes - I think the conclusions are more important for research (as in, more research needs to happen) than to clinicians. I think that common sense will still prevail that the risks of non-treatment outweigh any lack of evidence supporting that clinical decision.	The report authors acknowledge and appreciate the comment.
Peer Reviewer #6	General	General Comments: I appreciate the work that went into this review, but it is unbelievably long and no-one is going to read it all, subsequently the individual may miss some important information. I do not think it is clinically meaningful, because there is no bottom line which clinicians need and want, as basically, the authors say there is not enough information. If I was a psychiatrist confronted with a patient who needed treatment for depression in pregnancy, this document would not be of help, as it is so long and complicated and includes some information that clinicians just would not understand.	We can really appreciate these comments. It is hard to balance adequate details to respond to concerns as noted by other reviewers and to simplify the message. We hope the executive summary serves this purpose for some, and the abstract for others.
TEP Member #6	General	Clarity and Usability: As mentioned before, the report is much too long and convoluted and the main points are buried I don’t believe this document should be used for policy or practice decisions	The report authors acknowledge and appreciate the comment. We feel that both for clinical decisions and policy it is very important for decisionmakers to understand the limitations of the evidence. Better research may lead to Improved outcomes for pregnant and postpartum women.
TEP Member #7	General	The report is academically sound but of no practical use to clinicians who must decide which drugs to use to treat women with psychiatric disorders during pregnancy and postpartum.	The report authors acknowledge and appreciate the comment. We feel that both for clinical decisions and policy it is very important for decisionmakers to understand the limitations of the evidence. Better research may lead to Improved outcomes for pregnant and postpartum women.
TEP Member #7	General	Clarity and Usability: the report is far too long. The conclusions, that there are no gold standard studies and we need more, is irrelevant. We will never have these type of studies but have to make decisions based on what we have. this report gives no clear advice on how to make these decisions.	We do not agree that such studies cannot or will not be done – we found several and have pointed out that many of the existing observational studies could have used their existing data differently to answer the questions directly.

Commentator & Affiliation	Section	Comment	Response
TEP Member #8	General	General Comments: A superb review. It is clearly written, comprehensive, and methodologically sound. The key questions are appropriate and explicit, and the answers (or, more appropriately, the lack of answers) found in the literature are summarized in a way that identifies the lack of evidence for making clinical decisions, and identifies future research needs.	The report authors acknowledge and appreciate the comment.
TEP Member #9	General	Important review. Unfortunately not as helpful as we would like. Largely points out the gaps. Importance of registry data for both normal and adverse outcomes as RCT in this population unlikely.	The report authors acknowledge and appreciate the comment. As noted by other reviewers, RCT evidence is not out of the question in pregnant women, and is certainly possible in postpartum women. It may be that shifting the paradigm to comparisons of treatments that are currently being used is needed. Additionally, observational studies could be conducted in a way that provides direct comparative evidence in the population with depression.
TEP Member #9	General	Clarity and Usability: conclusions should point more for funding to answer the questions. registry data for all exposures not just harms.	The report authors acknowledge and appreciate the comment.
TEP Member #10	General	General Comments: Clinically meaningful: yes. Target population well-defined? Yes, however, P.32 (Scope and key questions) talks about the focus being on women who develop depression during pregnancy or the pp period, rather than those with a continuing episode. This point was not mentioned in the objectives in the Executive Summary, so this reviewer was caught off guard. First, there is no explanation as to why this should be the case. I would think it would limit the number of studies even more and there is already a paucity of evidence that meets inclusion criteria. Also, it didn't make sense to me clinically, as I don't think of pregnancy as a common time when women develop depression for the first time. Finally, this focus is not reflected in the analytic framework.	The report authors acknowledge and appreciate the comment. The report nominator and our technical expert panel introduced this criterion. However, while we wanted to identify new episodes of depression, most of the studies did not include information that could clearly define this population. They simply noted that the women were depressed or taking an antidepressant at the time of the study. Some included information on depression history, and a few were clear that the episode was a continuing one rather than a new episode. The applicability section was modified to include: "We were looking for evidence on women with a new episode (not necessarily the first) of depression during pregnancy or postpartum, rather than a continuing episode. The studies were unclear on this point and most simply identified women taking an antidepressant during pregnancy, with few identifying proportions of women with a history of depression, and even fewer reporting the number with a continuing episode. None analyzed results based on these characteristics. We believe that the evidence base applies to a mixed group, and does not reflect clearly one or the other."

Commentator & Affiliation	Section	Comment	Response
TEP Member #10	General	Clarity and Usability: Well structured: yes Well-organized: yes In general, with a few exceptions, the authors have achieve a very consistent and clear writing style. The conclusions may not be clear in guiding practice decisions. This is not the fault of the ER, but rather the dearth of high quality evidence to guide practice. What is clear is that the authors have articulate why so many of the studies were poor quality and therefore, provide a directive to future studies.	The report authors acknowledge and appreciate the comment.
TEP Member #11	General	yes, the report is clinically meaningful and the target population clearly defined. I think the key questions are clearly stated.	The report authors acknowledge and appreciate the comment.
TEP Member #11	General	Clarity and Usability: I am not sure how the conclusions change current practice or policy; rather, they reinforce a general ambiguity about risks and benefits. I think the real policy this report influences is the need for better research, registries, and how difficult it is to complete controlled studies on a large scale.	The report authors acknowledge and appreciate the comment. The report authors acknowledge and appreciate the comment. As noted by other reviewers, RCT evidence is not out of the question in pregnant women, and is certainly possible in postpartum women. It may be that shifting the paradigm to comparisons of treatments that are currently being used is needed. Additionally, observational studies could be conducted in a way that provides direct comparative evidence in the population with depression.